Ontario Health
Cancer Care Ontario

PET Six-Month Monitoring Report 2019-2

Evidence from Primary Studies and Systematic Reviews and Recommendations from Clinical Practice Guidelines July to December 2019

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Report Date: June 25, 2020

QUESTION

What is the role of positron emission tomography (PET) in the clinical management of patients with cancer, sarcoidosis, epilepsy, or dementia with respect to:

- Diagnosis and staging
- Assessment of treatment response
- Detection and restaging of recurrence
- Evaluation of metastasis

Outcomes of interest are survival, quality of life, prognostic indicators, time until recurrence, safety outcomes (e.g., avoidance of unnecessary surgery), and change in clinical management.

INTRODUCTION

In 2010, the Ontario PET Steering Committee (the Committee) requested that the Program in Evidence-Based Care (PEBC) provide regular updates to the Committee of recently published literature reporting on the use of PET in patients with cancer, sarcoidosis, epilepsy, or dementia. The PEBC recommended a regular monitoring program be implemented, with a systematic review of recent evidence conducted every six months. The Committee approved this proposal, and this is the 18th issue of the six-month monitoring reports. This report is intended to be a high-level, brief summary of the identified evidence, and not a detailed evaluation of its quality and relevance.

METHODS

Literature Search Strategy

Full-text articles published between July and December 2019 were systematically searched through MEDLINE and EMBASE for evidence from primary studies and systematic reviews. The search strategies used are available upon request to the PEBC.

Inclusion Criteria for Clinical Practice Guidelines

Any clinical practice guidelines that contained recommendations with respect to PET were included. Study design was not a criterion for inclusion or exclusion.

Pediatric studies were included in this report and will be included in subsequent reports. The decision to include them was made by the Committee based on the formation of a Pediatric PET Subcommittee that will explore and report on indications relating to PET in pediatric cancer.

Inclusion Criteria for Primary Studies

Articles were selected for inclusion in the systematic review of the evidence if they were fully published, English-language reports of studies that met the following criteria:

1. Studied the use of 18-fluorodeoxyglucose (FDG) PET in cancer, sarcoidosis, or epilepsy in humans.
2. Evaluated the use of the following radiopharmaceutical tracers:
    - ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTATOC, ^{68}Ga DOTATATE
    - ^{18}F-choline, ^{11}C-choline (prostate cancer)
    - ^{18}F-FET ([^{18}F]fluoroethyl-L-tyrosine) (brain)
    - ^{18}F-FLT ([^{18}F]3-deoxy-^{3}F-fluorothymidine) (various)
    - ^{18}F-MISO ([^{18}F]fluoromisonidazole) (hypoxia tracer)
    - ^{18}F-FAZA ([^{18}F]fluoroazomycin arabinoside) (hypoxia tracer)
    - ^{18}F-fluoride (more accurate than bone scanning)
    - ^{18}F-flurpiridaz (cardiac)
    - ^{18}F-florbetapir (Amyvid) (dementia imaging)
    - ^{18}F-FDOPA
    - ^{68}Ga-PSMA (prostate-specific membrane antigen)
    - ^{18}F-FACBC (fluciclovine)
3. Published as a full-text article in a peer-reviewed journal.
4. Reported evidence related to change in patient clinical management or clinical outcomes, or reported diagnostic accuracy of PET compared with an alternative diagnostic modality.
5. Used a suitable reference standard (pathological and clinical follow-up) when appropriate.
6. Included ≥12 patients for a prospective study/randomized controlled trial (RCT) or ≥50 patients (≥25 patients for sarcoma) for a retrospective study with the disease of interest.

Inclusion Criteria for Systematic Reviews

1. Reviewed the use of FDG PET/computed tomography (CT) in cancer, sarcoidosis, or epilepsy.
2. Contained evidence related to diagnostic accuracy; change in patient clinical management, clinical outcomes, or treatment response; survival; quality of life; prognostic indicators; time until recurrence; or safety outcome (e.g., avoidance of unnecessary surgery).

Exclusion Criteria

1. Letters and editorials.

RESULTS

Literature Search Results

Primary Studies and Systematic Reviews

Seventy-eight studies published between July and December 2019 met the inclusion criteria. A summary of the evidence from the 78 studies can be found in **Appendix 1: Summary of studies from July to December 2019**.

Breast Cancer

Two studies met the inclusion criteria [1,2]. FDG PET/CT using PERCIST to predict pathological response following neoadjuvant chemotherapy showed very high sensitivity (100%) and negative predictive value (NPV) (100%), but poor specificity (30.6%) and positive predictive value (PPV) (41.9%) [1]. In patients with invasive ductal carcinoma, both FDG PET/CT (94.4%) and magnetic resonance imaging (MRI) (97.3%) exhibited high NPV for excluding advanced axillary lymph node metastases after neoadjuvant chemotherapy [2].

Epilepsy

One study met the inclusion criteria [3]. The PPVs of FDG PET/CT and ^{123}I-iomazenil single photon emission computed tomography (IMZ-SPECT) for identifying the correct surgical site are 55% and 59%, respectively. The combination of these two examinations improved the PPV to 67%.

Esophageal Cancer

Four studies met the inclusion criteria [4-7]. In the preoperative staging of esophageal squamous cell carcinoma/adenocarcinoma with or without neoadjuvant therapy, FDG PET/CT displayed overall poor sensitivity but high specificity for assessing lymph node metastases across three studies [4-6]. Hamai et al. [4] examined FDG PET/CT before and after neoadjuvant chemoradiotherapy, Dellaportas et al. [5] evaluated FDG PET/CT pre-neoadjuvant chemotherapy, and Lopci et al. [6] looked at FDG PET/CT before surgery. The diagnostic performance of CT and endoscopic ultrasound (EUS) were also unsatisfactory. Similarly in early T-stage (Tis to T2) patients, preoperative FDG PET/CT (accuracy, 73.1%) and EUS (accuracy, 74.5%) both provided suboptimal performance in differentiating N0 from node-positive disease [7].

Gastrointestinal Cancer

Ten studies met the inclusion criteria [8-17]. In the diagnosis of colorectal cancer, FDG PET/CT was more specific (75.4% versus 68.4%) but less sensitive (65.0% versus 80.0%) than colonoscopy [8]. In the postoperative setting, an RCT demonstrated that the addition of FDG PET/CT to conventional monitoring strategy increased cost without decreasing the treatment failure rate (29.2% versus 23.7%; relative risk [RR],1.23, 95% confidence interval [CI], 0.80 to 1.88; p=0.34). However, the median time to diagnosis of unresectable recurrence was significantly shorter with FDG PET/CT (7.0 versus 14.3 months, p=0.026) [9]. In stage III colon cancer, early postoperative FDG PET/CT modified the staging and treatment of 13.4% of patients [10]. For the detection and localization of colorectal liver metastases, one meta-analysis found that FDG PET or PET/CT was more specific (pooled estimate: 93.9% versus 73.5%, p<0.001) than multidetector CT with comparable sensitivity but less sensitive (pooled estimate: 74.1% versus 93.1%, p<0.001) than gadoxetate disodium-enhanced MRI with comparable specificity [11]. For liver metastases from any primary malignancy, results from a meta-analysis [12] and a retrospective study [13] both showed improved diagnostic accuracy for FDG PET/MRI over FDG PET/CT. In patients treated for gastric malignancies, one study [14] presented data that supported the use of FDG PET/CT to detect recurrence while

another study [15] did not. In the differentiation of xanthogranulomatous cholecystitis from gallbladder cancer, contrast-enhanced ultrasound exhibited the best diagnostic performance amongst other imaging modalities that included FDG PET/CT, MRI, CT, and ultrasound [16]. In the staging of stomach cancer, FDG PET/CT outperformed diffusion weighted (DWI)-MRI [17].

Genitourinary Cancer

One study met the inclusion criteria [18]. FDG PET/CT (accuracy, 91%) outperformed conventional imaging (accuracy, 81%) in the identification of recurrent bladder cancer and upper tract urothelial cancer.

Gynecologic Cancer

Six studies met the inclusion criteria [19-24]. For the initial staging of endometrial cancer, FDG PET/MRI proved significantly more sensitive (50.0% versus 33.3%, p=0.015) and specific (100% versus 91.2%, p<0.001) than FDG PET/CT in detecting regional lymph node metastases. Furthermore, the overall accuracy (81.8% versus 45.9%, p<0.001) of myometrial invasion detection was significantly higher for FDG PET/MRI than it was for FDG PET/CT [19]. In patients suspected of recurrence, FDG PET/CT was superior to conventional imaging (e.g., contrast-enhanced CT [CeCT], MRI) in the definitive diagnosis of recurrent disease. Information provided by FDG PET/CT changed the therapeutic approach in 21.0% of patients [20]. Two studies quantified the impact of FDG PET/CT on chemoradiotherapy planning for patients with locally advanced cervical cancer. Overall, FDG PET/CT uncovered additional areas of nodal involvement that were not seen on CT/MRI. This resulted in a change in treatment strategy for 45.8% to 50.0% of patients [21,22]. One retrospective study included both endometrial and cervical cancer patients. The authors concluded that FDG PET/CT and CeCT have similar diagnostic performance in detecting pelvic nodal metastases but cannot obviate the need for surgical nodal staging [23]. In patients with suspected recurrent ovarian cancer, FDG PET/CT was able to detect and localize the recurrence with high accuracy (patient-based, 95.5%; lesion-based, 94.4%) [24].

Head and Neck Cancer

Ten studies met the inclusion criteria [25-34]. Five of the studies evaluated the use of FDG PET/CT in head and neck squamous cell carcinoma. In previously untreated patients, FDG PET/CT (100%) was found to be more accurate than CeCT (92.5%) in detecting nodal metastases [25]. However, overall staging (9.6% of cases) and treatment recommendations (5.8% of cases) were less frequently affected [26]. In patients treated with radiotherapy with or without chemotherapy, the sensitivity and specificity of FDG PET/CT for response assessment at the primary site ranged from 81.8% to 85.7% and 86.5% to 93.0%, respectively, whereas the sensitivity and specificity of FDG PET/CT for response assessment at the nodal sites ranged from 44.4% to 83.3% and 92.6% to 95.6%, respectively [27,28]. For those with incomplete response (NI-RADS category 2), the NPV of FDG PET/CT for excluding residual or locoregional tumour recurrence was suboptimal at 85% [29]. In the evaluation of thyroid nodules with indeterminate fine-needle aspiration cytology for surgery, FDG PET/CT was not reliable in discriminating malignant from benign lesions (pooled sensitivity, 74%; pooled specificity, 58%) [30]. In patients radically treated for differentiated thyroid carcinoma who presented with elevated levels of thyroglobulin, negative Iodine-131 whole-body scanning, and without any signs of clinical or other imaging techniques (e.g., CT, ultrasound) for tumour recurrence, FDG PET/CT revealed metabolic abnormalities that led to changes in treatment strategy in 33.5% of cases [31]. In the post-treatment surveillance of oropharyngeal squamous cell carcinoma, FDG PET/CT had a lower PPV and, thus, significantly more false-positive results for detecting residual or recurrent disease in patients treated with chemoradiotherapy

(31.1%) than in patients treated with primary surgery (54.7%) [32]. In the post-radiotherapy evaluation of nasopharyngeal cancer, FDG PET or PET/CT was prognostic for long-term treatment outcomes and showed a high NPV for excluding the presence of viable primary tumour (100%) or lymph nodes (99%) [33]. In patients with salivary gland carcinoma, FDG PET/CT did not provide any benefits in T-staging over MRI and chest x-ray, but it may be advantageous in N- and M-staging [34].

Hematologic Cancer

Thirteen studies met the inclusion criteria [35-47]. Six of the studies investigated the clinical utility of FDG PET/CT in Hodgkin lymphoma. Compared with CeCT, pretreatment FDG PET/CT led to an upstage in 9.1% and a downstage in 1.6% of patients, with a change of treatment in 8.1% of cases [35]. In particular, FDG PET/CT can reliably exclude bone marrow involvement (NPV, 99.9%) without the need for bone marrow biopsy [36]. In patients with early-stage favourable disease, a phase II trial (CALGB 50604) demonstrated that those with a negative interim FDG PET/CT scan treated with four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) without radiation therapy achieved a three-year progression-free survival (PFS) of 91% [37]. However, in the randomized phase III HD16 trial, the omission of involved-field radiotherapy from combined-modality treatment after two cycles of ABVD for interim-PET-negative patients resulted in poorer tumour control (hazard ratio [HR], 1.78; 95% CI, 1.02 to 3.12, which included the predefined noninferiority margin of 3.01) [38]. In patients with advanced-stage disease, using a Deauville score (DS) of four rather than three as the cut-off value for interim-PET positivity after two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses (eBEACOPP) is an important risk factor for survival outcomes [39]. Similarly in the elderly patient population (age ≥60 years), those with a positive interim FDG PET/CT scan (DS of 4 or 5) after two to three treatment cycles had significantly worse prognosis than their interim-PET-negative (DS of 1 to 3) counterparts [40]. Four retrospective studies looked at FDG PET/CT in non-Hodgkin lymphoma. In patients with diffuse large B-cell lymphoma, interim FDG PET/CT scan after two to four cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or rituximab, pirarubicin, cyclophosphamide, vincristine, and prednisone (R-THP-CHOP) displayed moderate NPV (71% to 75.8%) and low PPV (48% to 57.1%) for predicting disease progression. The predictive accuracies improved for end-of-treatment FDG PET/CT (NPV, 75.0% to 80%; PPV, 75.0% to 80%) [41,42]. In patients with newly diagnosed extranodal natural killer/T-cell lymphoma and taking routine bone marrow biopsy as the reference standard, the sensitivity and specificity of FDG PET/CT in assessing bone marrow involvement were 100% and 92.8%, respectively [43]. In the staging of mantle cell lymphoma, FDG PET/CT showed very high specificity for evaluating bone marrow (100%) and gastrointestinal tract (99%) involvement, but the sensitivities were suboptimal (27% and 60%, respectively) [44]. Three studies included patients with Hodgkin lymphoma and non-Hodgkin lymphoma. For identifying lymphomatous lymph nodes, there was no significant difference in accuracy between FDG PET/CT (88.6%), CeCT (80.7%), and contrast-enhanced ultrasound (83.6%) [45]. In patients with limited stage Hodgkin lymphoma and aggressive non-Hodgkin lymphoma on the basis of clinical data and CT, FDG PET/CT helped upstage 17.6% of cases. As a consequence, planned management was altered in 38.6% of patients [46]. In the post-treatment setting, FDG PET or PET/CT generated a high proportion of false-positive results (Hodgkin lymphoma, 35.2%; non-Hodgkin lymphoma, 49.4%) for monitoring disease recurrence or progression [47].

Melanoma

Five studies met the inclusion criteria [48-52]. In the staging of patients with melanoma, FDG PET/CT, FDG PET/MRI, and ultrasound all displayed poor sensitivity but high specificity for detecting nodal metastases prior to sentinel lymph node biopsy [48,49]. FDG PET/CT appeared to be reliable in restaging patients with metastatic spread of disease, where 17.8% of stage III patients were upstaged to stage IV disease. These patients were additionally treated with immunotherapy [50]. In the post-treatment setting, results from a meta-analysis showed that FDG PET or FDG PET/CT detected recurrence with high sensitivity (pooled estimate, 94%) and specificity (pooled estimate, 91%) [51]. Similar findings were reported from a retrospective study of only stage III patients [52].

Neuro-oncology

One study met the inclusion criteria [53]. A meta-analysis reported no significant difference in diagnostic performance between FDG PET or PET/CT (pooled sensitivity, 83%; pooled specificity, 88%) and MRI (pooled sensitivity, 84%; pooled specificity, 88%) for detecting tumour recurrence in patients with brain metastasis treated with stereotactic radiosurgery.

Non-FDG Tracers

Sixteen studies met the inclusion criteria [54-69]. One meta-analysis evaluated the role of ^{11}C- or ^{18}F-Choline PET or PET/CT in hepatocellular carcinoma while another meta-analysis explored ^{18}F-FCH PET/CT in prostate cancer. The pooled detection rate of ^{11}C- or ^{18}F-Choline PET or PET/CT on a per-patient and per-lesion based analysis were 83% and 79%, respectively [54]. In patients with newly diagnosed prostate cancer, ^{18}F-FCH PET/CT demonstrated low sensitivity (pooled estimate, 57%) but high specificity (pooled estimate, 94%) for lymph node staging [55]. In patients with pheochromocytoma and paraganglioma, ^{68}Ga-DOTA-TATE/NOC/TOC PET or PET/CT demonstrated superior performance over $^{123/131}$I-meta-iodobenzylguanidine (MIBG) scintigraphy for lesion detection (pooled estimate, 93% versus 38%, $p<0.0001$) [56]. In patients with neuroendocrine tumours, ^{68}Ga-DOTA-TATE PET/CT was associated with changes in treatment plans in 66% of cases [57]. The impact of amyloid PET on patients with cognitive impairment or dementia was quantified in three studies. Overall, amyloid PET contributed to diagnostic revision in 24.7% to 35.2% of patients and changed management in 24.3% to 72.2% of patients [58-60]. Several studies examined ^{68}Ga-PSMA-11 PET/CT in prostate cancer. Compared with serum prostate-specific antigen (PSA) (60.0%) and multiparametric MRI (66.6%), ^{68}Ga-PSMA-11 PET/CT (80.0%) had a higher diagnostic accuracy in predicting the presence or absence of malignancy [61]. Likewise, ^{68}Ga-PSMA-11 PET/CT was more sensitive and more accurate than technetium 99m-methyl diphosphonate (^{99m}Tc-MDP) bone scintigraphy in the evaluation of bone metastases. In addition, ^{68}Ga-PSMA-11 PET/CT detected soft tissue metastases in 12.4% of patients who had negative bone scans [62]. In terms of radiotherapy planning, ^{68}Ga-PSMA-11 PET/CT influenced the decision making in 13.0% to 16.4% of patients [63,64]. As for monitoring response to treatment, ^{68}Ga-PSMA-11 PET/CT guided further therapeutic management in 73.3% of patients [65]. The utility of ^{18}F-NaF PET/CT and ^{18}F-FACBC PET/CT were also evaluated in prostate cancer. For the detection bone metastases, the performance of ^{18}F-NaF PET/CT was comparable to that of DWI-MRI but was superior to both ^{99m}Tc-bone scintigraphy and 99mTc-SPECT [66]. On the other hand, ^{18}F-FACBC PET/CT appeared to have deficiencies in detecting recurrent disease [67] and regional lymph node metastases [68]. ^{18}F-FDOPA PET or PET/CT demonstrated a pooled sensitivity of 90% and a pooled specificity of 75% for diagnosing gliomas, and a pooled sensitivity of 88% and a pooled specificity of 73% for grading gliomas [69].

Pediatric Cancer

One study met the inclusion criteria [70]. FDG PET/CT (96%) was more sensitive than bone marrow biopsy (38%) in assessing bone marrow involvement in newly diagnosed pediatric Hodgkin lymphoma.

Sarcoidosis

One study met the inclusion criteria [71]. After FDG PET/CT examination, therapy was changed in 26.3% of patients with head and neck sarcoidosis. Patients were either given higher doses of corticosteroid or additional methotrexate along with prednisone.

Sarcoma

Three studies met the inclusion criteria [72-74]. One meta-analysis demonstrated that FDG PET or PET/CT is highly accurate in detecting recurrence (area under the curve [AUC], 0.95), lung metastases (AUC, 0.93), bone metastases (AUC, 0.98), and distant metastases (AUC, 0.96) in patients with osteosarcoma [72]. In another meta-analysis, FDG PET or PET/CT was found to be superior to Tc-99m MDP, Thallium-201 scintigraphy, and Tc99m-dimercaptosuccinic acid (DMSA) in the diagnosis of chondrosarcoma [73]. In the post-therapy surveillance of patients with uterine sarcoma, FDG PET/CT showed remarkable sensitivity (88%) and specificity (98%) for localizing recurrent disease. Additional information provided by FDG PET/CT modified clinical decision making for 19.5% of cases [74].

Thoracic Cancer

Four studies met the inclusion criteria [75-78]. For staging non-small cell lung cancer (NSCLC), FDG PET or PET/CT and chest CT were comparably accurate [75]. However, in post-treatment surveillance, FDG PET/CT was not superior to CeCT in detecting recurrence during the two-year follow-up period [76]. For differentiating between malignant and benign pulmonary lesions, DWI-MRI showed superior sensitivity (summary estimate: 83% versus 78%, p=0.018), diagnostic odds ratio (summary estimate: 50 versus 15, p=0.001), and AUC (summary estimate: 0.93 versus 0.86, p=0.001) over FDG PET/CT [77]. In post-surgery surveillance of malignant pleural mesothelioma, FDG PET/CT was found to be significantly more accurate than CeCT in detecting tumour recurrence (AUC, 0.915 versus 0.805, p=0.041), thoracic recurrence (accuracy, 90.0% versus 76.0%, p=0.023), lymph node involvement (accuracy, 92.0% versus 80.0%, p=0.041), and distant metastases (AUC, 0.957 versus 0.852, p=0.035). FDG PET/CT findings led to subsequent changes in therapy in 28.0% of patients [78].

CLINICAL EXPERT REVIEW

Breast Cancer

Current Eligibility Criteria for the PET ABC Trial

- For the staging of patients with clinical stage III breast cancer.

Reviewer's Comments

A review was not completed by a clinical expert in breast cancer.

Epilepsy

Current Indication for Epilepsy

- For patients with medically intractable epilepsy being assessed for epilepsy surgery.

Reviewer's Comments (Dr. Jorge Burneo)

The current recommendations for the utilization of PET/CT in epilepsy remain valid and no changes are required.

Esophageal Cancer

Current Indications for Esophageal Cancer

- For baseline staging assessment of those patients diagnosed with esophageal/ gastroesophageal junction cancer being considered for curative therapy and/or repeat PET/CT scan on completion of preoperative/neoadjuvant therapy, prior to surgery; or for re-staging of patients with locoregional recurrence, after primary treatment, being considered for definitive salvage therapy.

Reviewer's Comments (Dr. Rebecca Wong)

The current recommendations for the utilization of PET/CT in esophageal cancer remain valid and no changes are required.

Gastrointestinal Cancer

Current Indications for Colorectal Cancer

- For the staging or re-staging of patients with apparent limited metastatic disease (e.g., organ-restricted liver or lung metastases) or limited local recurrence, who are being considered for radical intent therapy.
  Note: as chemotherapy may affect the sensitivity of the PET scan, it is strongly recommended to schedule PET at least six weeks after last chemotherapy, if possible.
- Where recurrent disease is suspected on the basis of an elevated and/or rising carcinoembryronic antigen level(s) during follow-up after surgical resection but standard imaging tests are negative or equivocal.

Current Indication for Anal Canal Cancer

- For the initial staging of patients with T2-4 (or node positive) squamous cell carcinoma of the anal canal with or without evidence of nodal involvement on conventional anatomical imaging.

Reviewer's Comments

A review was not completed by a clinical expert in gastrointestinal cancer.

Genitourinary Cancer

Current Indications for Germ Cell Tumours

- Where recurrent disease is suspected on the basis of elevated tumour marker(s) (beta human chorionic gonadotropin and/or alpha fetoprotein) and standard imaging tests are negative; or where persistent disease is suspected on the basis of the presence of a residual mass after primary treatment for seminoma when curative surgical resection is being considered.

Current Eligibility Criteria for the PET MUSE Trial

- For the staging of patients with muscle-invasive urothelial carcinoma of the bladder.

Reviewer's Comments (Dr. Glenn Bauman)

The current recommendations for the utilization of PET/CT in genitourinary cancer remain valid and no changes are required as we are awaiting the completion of the PET MUSE trial, which will provide higher quality data.

Gynecologic Cancer

Current Indications for Cervical Cancer

- For the staging of locally advanced cervical cancer when CT/MRI shows positive or indeterminate pelvic nodes (>7 mm and/or suspicious morphology), borderline or suspicious para-aortic nodes, or suspicious or indeterminate distant metastases (e.g., chest nodules).
- For re-staging of patients with recurrent gynecologic malignancies under consideration for radical salvage surgery (e.g., pelvic exenteration).

Reviewer's Comments

A review was not completed by a clinical expert in gynecologic cancer.

Head and Neck Cancer

Current Indications for Head and Neck Cancer

- For the baseline staging of node positive (N1-N3) head and neck cancer where PET will impact radiation therapy (e.g., radiation volume or dose).
- To assess patients with N1-N3 metastatic squamous-cell carcinoma of the head and neck after chemoradiation (human papillomavirus [HPV] negative); or who have residual neck nodes equal to or greater than 1.5 cm on re-staging CT performed 10 to12 weeks post therapy (HPV positive).

Current Indication for Unknown Primary

- For the evaluation of metastatic squamous cell carcinoma in neck nodes when the primary disease site is unknown after standard radiologic and clinical investigation.
  Note: a panendoscopy is not required prior to the PET scan.

Current Indication for Nasopharyngeal Cancer

- For the staging of nasopharyngeal cancer.

Current Indications for Thyroid Cancer

- Where recurrent or persistent disease is suspected on the basis of an elevated and/or rising tumour markers (e.g., thyroglobulin) with negative or equivocal conventional imaging work-up.
- For the staging of histologically proven anaplastic thyroid cancer with negative or equivocal conventional imaging work-up.
- For the baseline staging of histologically proven medullary thyroid cancer being considered for curative intent therapy or where recurrent disease is suspected on the basis of elevated and/or rising tumour markers (e.g., calcitonin) with negative or equivocal conventional imaging work-up.

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendations for the utilization of PET/CT in head and neck cancer remain valid and no changes are required.

Hematologic Cancer

Current Indications for Lymphoma

- For the baseline staging of patients with Hodgkin or non-Hodgkin lymphoma.
- For the assessment of response in Hodgkin lymphoma following two or three cycles of chemotherapy when curative therapy is being considered.
- For the evaluation of residual mass(es) or lesion(s) (e.g., bone) following chemotherapy in a patient with Hodgkin or non-Hodgkin lymphoma when further

potentially curative therapy (such as radiation or stem cell transplantation) is being considered.

Current Indications for Multiple Myeloma or Plasmacytoma

- For patients with presumed solitary plasmacytoma who are candidates for curative intent radiotherapy (to determine whether solitary or multifocal/extensive disease).
- For work-up of patients with smoldering myeloma and negative or equivocal skeletal survey (to determine whether smoldering or active myeloma).
- For baseline staging and response assessment.

Reviewer's Comments

A review was not completed by a clinical expert in hematologic cancer.

Melanoma

Current Indications for Melanoma

- For the staging of patients with localized "high-risk" melanoma, or for the evaluation of patients with isolated melanoma metastases, when surgery or other ablative therapies are being considered.

Reviewer's Comments (Dr. Tara Baetz)

The current recommendations for the utilization of PET/CT in melanoma remain valid and no changes are required. The study by Schaarschmid et al. [48] showed that PET/CT does not replace sentinel node biopsy, whereas the Groen et al. [50] study indicated that patients are often upstaged by PET/CT especially with head and neck primary.

The study by Lewin et al. [52], albeit retrospective, is very compelling for PET/CT in the surveillance of patients with stage III melanoma after treatment. PET/CT was approved every six months for the first two years followed by one additional scan a year later. The sensitivity and specificity were very high and 52% of patients found with metastases were able to have a curative resection. Since PET/CT was able to detect mostly symptomatic cases, patients can be managed early and aggressively. The Cochrane review by Dinnes et al. [49] is very thorough and suggested that really good trials are lacking in the current era of melanoma treatment but that PET/CT is able to correctly identify patients with metastatic spread, particularly in the restaging scenario (as opposed to the current indications for primary staging and for isolated disease). Lee et al. [51] is also a review of surveillance studies and indicated that PET or PET/CT has a high sensitivity and specificity for recurrence in high-risk melanoma. Thus, based on the above studies, it may be worthwhile to consider adding surveillance PET/CT in high-risk disease (stage IIIB-C) for up to three years post-surgery.

Neuro-oncology

Current indication for Paraneoplastic Syndrome

- For the evaluation of patients with suspected paraneoplastic neurologic syndromes with negative conventional imaging, with or without positive onconeuronal antibodies.

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendations for the utilization of PET/CT in neuro-oncology remain valid and no changes are required.

Non-FDG Tracers

Current Indications for Gallium-68 PET/CT in Neuroendocrine Tumours

- For identification of primary tumour when there is clinical suspicion of neuroendocrine tumours and primary tumour site is unknown or uncertain.
- For the staging of patients upon initial presentation of neuroendocrine tumours.
- For the re-staging of patients with neuroendocrine tumours when clinical intervention is being considered.
- As a problem-solving tool in patients with neuroendocrine tumours when confirmation of site of disease and/or disease extent may impact clinical management.

Current Indications for PSMA PET/CT in Prostate Cancer

- For patients with post-prostatectomy node-positive disease or persistently detectable PSA.
- For patients with biochemical failure post-prostatectomy.
- For patients with failure following radical prostatectomy followed by adjuvant or salvage radiotherapy.
- For patients with rising PSA post-prostatectomy despite salvage hormone therapy.

Reviewer's Comments (Dr. Amit Singnurkar)

The current recommendations for the utilization of PET/CT with non-FDG tracers remain valid and no changes are required. Current indications for neuroendocrine tumours and prostate cancer account for most of these findings. The ^{18}F-FDOPA article Xiao et al. [69] again provides compelling evidence for its use in neuro-oncology. This is an amino acid tracer, similar to ^{18}F-FET, that we want to explore further as discussed previously. This article may have some references for our eventual review of ^{18}F-FET.

Pediatric Cancer

Current Indications for Pediatric Cancer (patients must be <18 years of age)

- For the following cancer types (International Classification for Childhood Cancer):
    - Bone/cartilage – osteosarcoma, Ewing sarcoma
    - Connective/other soft tissue – rhabdomyosarcoma, other
    - Kidney – renal tumour
    - Liver – hepatic tumour
    - Lymphoma/post-transplant lymphoproliferative disorder – Hodgkin lymphoma and non-Hodgkin lymphoma
    - Primary brain – astrocytoma, medulloblastoma, ependymoma, other
    - Reproductive – germ cell tumour
    - Sympathetic nervous system - neuroblastoma MIBG-negative
    - Other – Langerhans cell histiocytosis, melanoma of the skin, thyroid
- For the following indications:
    - Initial staging
    - Monitoring response during treatment/determine response-based therapy
    - Rule out progression prior to further therapy
    - Suspected recurrence/relapse
    - Rule out persistent disease
    - Select optimal biopsy site

Reviewer's Comments (Dr. Amer Shammas)

The current recommendations for the utilization of PET/CT in pediatric cancer remain valid and no changes are required.

Sarcoidosis

- No indication currently exists for the utilization of PET/CT in sarcoidosis.

Reviewer's Comments (Dr. Bob Hyland)

There is currently not enough evidence to support making appropriate recommendations for the use of PET/CT in sarcoidosis. However, there needs to be a prospective Canadian study to look at the efficacy of PET/CT scanning in the diagnosis and follow-up of patients with sarcoidosis. This is a complex multisystem disease and the treatment is not without significant complications.

Sarcoma

Current Indications for Sarcoma

- For patients with suspicion of malignant transformation of plexiform neurofibromas.
- For patients with high-grade (≥grade 2), or ungradable, soft tissue or bone sarcomas, with negative or equivocal findings for nodal or distant metastases on conventional imaging, prior to curative intent therapy.
- For patients with history of treated sarcoma with suspicion of, or confirmed, recurrent sarcoma (local recurrence or limited metastatic disease) being considered for curative intent or salvage therapy.

Reviewer's Comments

A review was not completed by a clinical expert in sarcoma.

Thoracic Cancer

Current Indications for Solitary Pulmonary Nodule

- For a semi-solid or solid lung nodule for which a diagnosis could not be established by a needle biopsy due to unsuccessful attempted needle biopsy; the solitary pulmonary nodule is inaccessible to needle biopsy; or the existence of a contra-indication to the use of needle biopsy.

Current Indications for NSCLC

- For initial staging of patients with NSCLC (clinical stage I – III) being considered for potentially curative therapy.
- For re-staging of patients with locoregional recurrence, after primary treatment, being considered for definitive salvage therapy.
  Note: Histological proof is not required prior to PET if there is high clinical suspicion for NSCLC (e.g., based on patient history and/or prior imaging).
  Note: PET is appropriate for patients with either histological proof of locoregional recurrence or strong clinical and radiological suspicion of recurrence who are being considered for definitive salvage therapy.

Current Indication for small cell lung cancer

- For initial staging of patients with limited disease small cell lung cancer where combined modality therapy with chemotherapy and radiotherapy is being considered.

Current Indication for Mesothelioma

- For the staging of patients with histologic confirmation of malignant mesothelioma.

Reviewer's Comments (Dr. Donna Maziak)

The current recommendations for the utilization of PET/CT in thoracic cancer remain valid and no changes are required. However, it may be worthwhile to expand the recommendations to include the use of PET/CT in the follow-up of lung cancer and in post-treatment surveillance of mesothelioma.

Funding

The PEBC is a provincial initiative of Ontario Health (Cancer Care Ontario) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

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Appendix 1: Summary of studies from July to December 2019.

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Breast Cancer								
Kitajima et al, 2018 [1]	Retrospective	56 patients who underwent response assessment before and after neoadjuvant chemotherapy prior to planned surgical resection (breast cancer)	FDG PET/CT	NA	Histopathology	**Predicting pathological response using (PERCIST)** Sens: 100% Spec: 30.6% PPV: 41.9% NPV: 100% Accu: 53.7% **(SULpeak of 84.3%)** Sens: 77.8% Spec: 77.8% PPV: 63.6% NPV: 87.5% Accu: 77.8%	NA	NA
Kim et al, 2018 [2]	Retrospective	108 patients who underwent initial staging and restaging after neoadjuvant chemotherapy followed by axillary surgery (invasive ductal carcinoma)	FDG PET/CT	MRI	Histopathology	**Predicting advanced axillary lymph node metastases** Sens: 58.3% Spec: 87.5% PPV: 36.8% NPV: 94.4% AUC: 0.729	**Predicting advanced axillary lymph node metastases** Sens: 83.3% Spec: 75.0% PPV: 29.4% NPV: 97.3% AUC: 0.792	NA
Epilepsy								
Fujimoto et al, 2018 [3]	Retrospective	59 patients who underwent subdural electrode implantation followed by focus resection (refractory epilepsy)	FDG PET/CT	MRI, EEG, VEEG, IMZ-SPECT, seizure semiology	Epileptogenic zone determined at case conferences	**Concordant with surgical sites** PPV: 55%	**Concordant with surgical sites** ***IMZ-SPECT*** PPV: 59%	NA
Esophageal Cancer								
Hamai et al, 2019 [4]	Retrospective	132 patients treated with neoadjuvant chemoradiother	FDG PET/CT (pre- and post-	CT, esophagography, endoscopy	Pathology	**Lymph node metastases** **Before neoadjuvant chemoradiotherapy**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		apy followed by surgery (locally advanced esophageal squamous cell carcinoma)	neoadjuvant chemoradiotherapy)			**(patient-based)** Sens: 84.5% Spec: 40.5% Accu: 59.8% **(station-based)** Sens: 41.7% Spec: 95.0% Accu: 92.7% **After neoadjuvant chemoradiotherapy (patient-based)** Sens: 27.6% Spec: 87.8% Accu: 61.4% **(station-based)** Sens: 12.0% Spec: 99.4% Accu: 95.6%		
Dellaportas et al, 2019 [5]	Retrospective	151 patients who underwent staging before neoadjuvant chemotherapy and esophagectomy (esophageal adenocarcinoma)	FDG PET/CT (pre-neoadjuvant chemotherapy)	EUS	Histopathology	**Lymph node metastases** Sens: 39.2% Spec: 83.3% Accu: 55.0%	**Lymph node metastases** Sens: 88.6% Spec: 19.2% Accu: 62.7%	NA
Lopci et al, 2019 [6]	Retrospective	101 patients who underwent surgery (Siewert type I/II oesophageal adenocarcinoma)	FDG PET/CT (pre-surgery)	CT, EUS	Pathology	**Lymph node metastases** Sens: 30% Spec: 98% PPV: 74% NPV: 58%	**Lymph node metastases** ***CT*** Sens: 39% Spec: 86% PPV: 74% NPV: 58% ***EUS*** Sens: 50% Spec: 81% PPV: 62% NPV: 72%	NA
Jeong et al, 2018 [7]	Retrospective	435 patients who received esophagectomy and lymph node dissection (Tis-T2 esophageal	FDG PET/CT (pre-surgery)	EUS	Histopathology	**Discriminating N0 from node-positive disease** Sens: 88.9% Spec: 38.7% PPV: 75.9%	**Discriminating N0 from node-positive disease** Sens: 89.6% Spec: 41.6% PPV: 76.9%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		squamous cell carcinoma)				NPV: 61.6% Accu: 73.1%	NPV: 64.8% Accu: 74.5%	
Gastrointestinal Cancer								
Nowicki et al, 2019 [8]	Retrospective	125 patients with symptoms from the lower gastrointestinal tract (colorectal cancer)	FDG PET/CT	Colonoscopy	Histopathology	**Diagnosis** Sens: 65.0% Spec: 75.4% Accu: 72.7%	**Diagnosis** Sens: 80.0% Spec: 68.4% Accu: 71.4%	NA
Sobhani et al, 2018 [9]	RCT	239 patients who underwent curative surgery (colorectal cancer at risk for recurrence)	FDG PET/CT with CI (n=120)	physical and tumour marker assays, liver US, chest radiography, whole-body CT (n=119)	Biopsy, follow-up, multidisciplinary meeting	NA	NA	The frequency of treatment failure did not significantly differ between arms (w/ PET/CT, 29.2% vs. w/o PET/CT, 23.7%; RR=1.23; 95% CI: 0.80 to 1.88; p=0.34). Median time to diagnosis of unresectable recurrence was significantly shorter with PET/CT (7.0 vs. 14.3 months; p=0.026).
Moore et al, 2018 [10]	Retrospective	342 patients who underwent a curative resection (stage III colon cancer)	FDG PET/CT	NA	Biopsy, imaging follow-up	NA	NA	Early postoperative PET/CT modified the management of 13.4% (46/342) of patients (9—discovered second primary tumours, 14—treated with curative intent, 23—treated with palliative intent).
Choi et al, 2018 [11]	Meta-analysis	24 studies (patients with colorectal liver metastasis)	FDG PET or PET/CT	MDCT, gadoxetate disodium-enhanced MRI	Pathology, intraoperative US, radiological methods	**Diagnosis** Pooled Sens: 74.1%* Pooled Spec: 93.9%*	**Diagnosis** ***MDCT*** Pooled Sens: 82.1% Pooled Spec: 73.5%* ***Gadoxetate disodium-enhanced MRI*** Pooled Sens: 93.1%* Pooled Spec: 87.3%	NA
Hong et al, 2019 [12]	Meta-analysis	8 studies (1123 lesions; 179 patients with suspected liver metastases from any primary	FDG PET/CT or PET/MRI	NA	Pathology, imaging follow-up	**Liver metastases (patient-based)** ***FDG PET/MRI*** Pooled Sens: 99.2% Pooled Spec: 98.6% **(lesion-based)**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		malignancy)				***FDG PET/MRI*** Pooled Sens: 95.4%‡ Pooled Spec: 99.3% ***FDG PET/CT*** Pooled Sens: 68.3%‡ Pooled Spec: 95.7%		
Parsai et al, 2019 [13]	Retrospective	70 patients with indeterminate liver lesions after CT and US (suspected liver metastases)	FDG PET/CT or PET/MRI	MRI	Histopathology, imaging follow-up, surgical report	**Malignant lesions** ***PET/CT*** Sens: 55.6% Spec: 83.3% PPV: 84.2% NPV: 57.1% Accu: 66.7% AUC: 0.82 ***PET/MRI*** Sens: 91.9% Spec: 97.4% PPV: 97.1% NPV: 92.5% Accu: 94.7% AUC: 0.94	**Malignant lesions** Sens: 67.6% Spec: 92.1% PPV: 89.3% NPV: 74.5% Accu: 80.0% AUC: 0.92	NA
Elfattah Hassan Gadalla et al, 2019 [14]	Retrospective	50 patients treated with surgery (suspected recurrent gastric cancer)	FDG PET/CT	CT, MRI	Histopathology, biopsy, clinical or imaging follow-up	**Locoregional recurrence** Sens: 75.0% Spec: 81.6% PPV: 56.3% NPV: 91.2% Accu: 80.0% **Regional lymph node recurrence** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100% **Liver metastases** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100% **Peritoneum metastases** Sens: 100% Spec: 97.3% PPV: 92.9%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						NPV: 100% Accu: 98.0% **Distant metastases** Sens: 100% Spec: 85.7% PPV: 90.6% NPV: 100% Accu: 94.0%		
Baz et al, 2019 [15]	Retrospective	68 patients who underwent follow-up after treatment (gastric malignancy)	FDG PET/CT	CeCT	Clinical and imaging follow-up	**Residual/recurrent disease** Sens: 44.0%* **Lymph node metastases** Sens: 26.5% **Distant metastases** Sens: 26.5%	**Residual/recurrent disease** Sens: 67.5%* **Lymph node metastases** Sens: 38.0% **Distant metastases** Sens: 35.0%	NA
Bo et al, 2019 [16]	Retrospective	218 patients who underwent surgery (xanthogranulomatous cholecystitis or gallbladder cancer)	FDG PET/CT	MRI, CT, CeUS, US	Histopathology	**Differential diagnosis** Sens: 55% Spec: 90% PPV: 80% NPV: 73%	**Differential diagnosis** ***MRI*** Sens: 75% Spec: 90% PPV: 88% NPV: 78% ***CT*** Sens: 71% Spec: 92% PPV: 82% NPV: 86% ***CeUS*** Sens: 90% Spec: 93% PPV: 86% NPV: 94% ***US*** Sens: 80% Spec: 86% PPV: 85% NPV: 81%	NA
Sui et al, 2019 [17]	Retrospective	160 patients (stomach cancer)	FDG PET/CT	DWI-MRI	Pathology	**Staging (I-II)** Sens: 85.3%* Spec: 81.5%* Accu: 83.8%* **Staging (III-IV)** Sens: 81.5% Spec: 85.3%* Accu: 83.8%	**Staging (I-II)** Sens: 61.1%* Spec: 64.6%* Accu: 62.5%* **Staging (III-IV)** Sens: 80.0% Spec: 71.6%* Accu: 75.0%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Genitourinary Cancer								
Zattoni et al, 2018 [18]	Retrospective	287 patients who underwent primary treatment (suspected recurrent urothelial carcinoma)	FDG PET/CT	Abdomen and pelvis CeCT or MRI, whole-body CeCT, chest x-ray	Histopathology, clinical and imaging follow-up	**Recurrence (patient-based)** Sens: 94% Spec: 79% PPV: 95% NPV: 76% Accu: 91% **Local (lesion-based)** Sens: 22% Spec: 95% PPV: 94% NPV: 26% Accu: 38% **abdominopelvic lymph nodes (lesion-based)** Sens: 60% Spec: 95% PPV: 97% NPV: 40% Accu: 67% **Bone (lesion-based)** Sens: 24% Spec: 95% PPV: 94% NPV: 26% Accu: 40% **Lung (lesion-based)** Sens: 21% Spec: 95% PPV: 94% NPV: 26% Accu: 38% **Liver (lesion-based)** Sens: 15% Spec: 100% PPV: 100% NPV: 25% Accu: 34% **Other[µ] (lesion-based)**	**Recurrence (patient-based)** Sens: 86% Spec: 59% PPV: 90% NPV: 51% Accu: 81% **Local (lesion-based)** Sens: 23% Spec: 87% PPV: 88% NPV: 22% Accu: 36% **abdominopelvic lymph nodes (lesion-based)** Sens: 42% Spec: 95% PPV: 97% NPV: 29% Accu: 52% **Bone (lesion-based)** Sens: 15% Spec: 97% PPV: 96% NPV: 22% Accu: 31% **Lung (lesion-based)** Sens: 21% Spec: 77% PPV: 79% NPV: 19% Accu: 32% **Liver (lesion-based)** Sens: 6% Spec: 100% PPV: 100% NPV: 21% Accu: 25% **Other[µ] (lesion-based)**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Sens: 16% Spec: 100% PPV: 100% NPV: 25% Accu: 35%	Sens: 12% Spec: 97% PPV: 95% NPV: 21% Accu: 29%	
Gynecologic Cancer								
Bian et al, 2019 [19]	Retrospective	81 patients who underwent initial staging; 37 PET/CT, 44 PET/MRI (biopsy-proven endometrial cancer)	FDG PET/CT or PET/MRI	NA	Histopathology	**Primary tumour** ***PET/CT*** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100% ***PET/MRI*** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100% **Regional lymph node metastases** ***PET/CT*** Sens: 33.3%‡ Spec: 91.2%‡ PPV: 75.0% NPV: 93.9% Accu: 86.5% ***PET/MRI*** Sens: 50.0%‡ Spec: 100%‡ PPV: 100% NPV: 95.2% Accu: 95.5% **Abdominal metastases** ***PET/CT*** Sens: 100% Spec: 97.3% PPV: 100% NPV: 100% Accu: 97.3% ***PET/MRI*** Sens: 100% Spec: 100% PPV: 100% NPV: 100%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Accu: 100% **Myometrial invasion** ***PET/CT*** Accu: 45.9%‡ ***PET/MRI*** Accu: 81.8%‡		
Albano et al, 2019 [20]	Retrospective	157 patients who underwent restaging (suspected recurrent endometrial carcinoma)	FDG PET/CT	CeCT, MRI	Histopathology, clinical and imaging follow-up	**Recurrence** Sens: 96% Spec: 99% PPV: 99% NPV: 96% Accu: 97% +LR: 73.19 -LR: 0.04	**Recurrence** Sens: 97% Spec: 62% PPV: 72% NPV: 96% Accu: 80% +LR: 2.57 -LR: 0.04	PET/CT impacted the therapeutic approach in 21.0% (33/157) of patients (28—avoided unnecessary invasive therapies, 5—switched from local therapy to chemotherapy).
Waldenstrom et al, 2018 [21]	Prospective	25 patients who were planned for definitive radiochemotherapy (uterine cervical cancer stages IB2-IIIB)	FDG PET/CT	MRI	Imaging and clinical follow-up	NA	NA	PET/CT detected areas of nodal tumour spread that were not seen on MRI and changed treatment strategy in 45.8% (11/24) of patients (8—extended para-aortic fields, 3—extended treatment volume and/or increased dose).
Draghini et al, 2019 [22]	Prospective	14 patients who underwent definitive chemo-radiotherapy with IMRT and SIB (locally advanced cervical cancer)	FDG PET/CT	CT, MRI	Clinical and imaging follow-up	NA	NA	PET/CT uncovered evidence of nodal involvement that were not seen on CT/MRI in 50% (7/14) of patients. Subsequently, radiotherapy field size and doses were changed in these patients.
Zade et al, 2019 [23]	Prospective	72 patients (44 FIGO Stage 1A2-IIb carcinoma cervix; 28 FIGO Stage I-II carcinoma endometrium)	FDG PET/CT	CeCT	Histology	**Pelvic nodal metastases** Sens: 73% Spec: 89% PPV: 65% NPV: 93% Accu: 86% **Para-aortic nodal metastases** Sens: 50% Spec: 96% PPV: 40%	**Pelvic nodal metastases** Sens: 67% Spec: 89% PPV: 62% NPV: 91% Accu: 85% **Para-aortic nodal metastases** Sens: 50% Spec: 99% PPV: 67%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						NPV: 97% Accu: 93%	NPV: 97% Accu: 96%	
ElHariri et al, 2019 [24]	Prospective	36 patients (suspected recurrent ovarian cancer)	FDG PET/CT	US, CT, MRI, CA-125 levels	Histopathology, clinical and imaging follow-up	**Recurrence (patient-based)** Sens: 85.7% Spec: 97.9% PPV: 90.5% NPV: 97.0% Accu: 95.8% **(lesion-based)** Sens: 96.9% Spec: 75.0% PPV: 96.8% NPV: 75.0% Accu: 94.4%	NA	NA
Head and Neck Cancer								
Jain et al, 2019 [25]	Prospective	40 patients who underwent primary staging (head and neck squamous cell carcinoma)	FDG PET/CT	CeCT	Histopathology	**Nodal metastases** Sens: 100% Spec: 100% PPV: 100% NPV: 100% Accu: 100%	**Nodal metastases** Sens: 97.4% Spec: 0% PPV: 94.9% NPV: 0% Accu: 92.5%	NA
Jorgensen et al, 2019 [26]	Prospective	52 patients with clinical evidence of regional lymph node metastases (newly diagnosed advanced head and neck squamous cell carcinoma)	FDG PET/CT	Physical examination with or without endoscopy or panendoscopy, biopsy, CT, chest x-ray, serologic testing	Pre- and post-questionnaire	NA	NA	PET/CT changed the overall stage of 9.6% (5/52) of patients and altered treatment recommendations from primary concurrent chemoradiotherapy to palliative therapy in 5.8% (3/52) of patients.
Noij et al, 2018 [27]	Retrospective	82 patients treated with radiotherapy with or without chemotherapy (advanced-stage head and neck squamous cell carcinoma)	FDG PET/CT	DWI-MRI	Clinical and imaging follow-up	**Response assessment** **Primary tumour** Sens: 85.7% Spec: 86.5% PPV: 37.5% NPV: 98.5% AUC: 0.934 **Lymph node** Sens: 83.3% Spec: 92.6%* PPV: 50.0% NPV: 98.4%	**Response assessment** **Primary tumour** Sens: 57.1% Spec: 91.9% PPV: 40.0% NPV: 95.8% AUC: 0.759 **Lymph node** Sens: 100% Spec: 72.1%* PPV: 24.0% NPV: 100%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						AUC: 0.952	AUC: 0.855	
Ghosh-Laskar et al, 2019 [28]	Prospective	54 patients treated with chemoradiotherapy or radiotherapy only (head and neck squamous cell carcinoma)	FDG PET/CT	Clinical examination	Histopathology, clinical and imaging follow-up	**Response assessment** **Primary tumour** Sens: 81.8% Spec: 93.0% PPV: 75.0% NPV: 95.2% Accu: 90.7% **Lymph node** Sens: 44.4% Spec: 95.6% PPV: 66.7% NPV: 89.6% Accu: 87.0%	NA	NA
Wangaryattawanich et al, 2018 [29]	Retrospective	110 patients with an incomplete response (NI-RADS category 2) after primary definitive chemoradiation or radiation therapy (head and neck squamous cell carcinoma)	FDG PET/CT	NA	Histopathology, clinical and imaging follow-up	**Locoregional recurrence** NPV: 85%	NA	NA
Castellana et al, 2019 [30]	Meta-analysis	8 studies (438 thyroid nodules with indeterminate FNA cytology)	FDG PET/CT	FNA cytology	Histology	**Differentiating malignant from benign nodules (nodule-based)** Pooled Sens: 74% Pooled Spec: 58% Pooled PPV: 34% Pooled NPV: 74% Pooled +LR: 1.7 Pooled –LR: 0.4 Pooled DOR: 3.5	NA	NA
Larg et al, 2019 [31]	Retrospective	173 patients with elevated Tg levels, negative I-131 WBS, CT, and US after thyroidectomy and radioiodine	FDG PET/CT	Serum Tg levels, I-131 WBS, CT, US	Histopathology, clinical and imaging follow-up	**Recurrence or metastases** Sens: 88.1% Spec: 98.6% PPV: 93.1% NPV: 97.2% Accu: 96.5%	NA	PET/CT altered clinical management in 33.5% (58/173) of patients (29—underwent surgery, 24—continued radioiodine therapy, 3—referred for tyrosine kinase inhibitors

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		therapy (differentiated thyroid carcinoma)						treatment, 2—initiated external radiotherapy).
Sivarajah et al, 2018 [32]	Retrospective	190 patients treated with primary surgery with or without adjuvant therapy or primary chemoradiotherapy (oropharyngeal squamous cell carcinoma)	FDG PET/CT	NA	Histopathology, radiographic clearance, clinical correlation	**Residual and/or recurrent disease** Sens: 93.3% Spec: 57.9% PPV: 54.7%, surgery; 31.1%, chemoradiotherapy NPV: 100%, surgery; 96.6%, chemoradiotherapy DOR: 19.3	NA	NA
Jeong et al, 2019 [33]	Retrospective	143 patients who underwent post-radiotherapy evaluation (non-disseminated nasopharyngeal cancer)	FDG PET or PET/CT	NA	Histopathology, clinical or imaging follow-up	**Residual disease** **Primary tumour** Sens: 100% Spec: 84% PPV: 8% NPV: 100% **Lymph node** Sens: 67% Spec: 80% PPV: 7% NPV: 99%	NA	The 5-year OS (44 vs. 86%, p=0.004) and DMFS (36% vs. 85%, p<0.001) rates were significantly lower for patients with positive PET findings at regional lymph nodes than those with negative PET findings.
Westergaard-Nielsen [34]	Prospective	91 patients underwent primary staging prior to surgery (salivary gland carcinoma)	FDG PET/CT	MRI, chest x-ray	Histopathology	**Primary tumour** Sens: 92% Spec: 29% PPV: 60% NPV: 75% Accu: 63% **Cervical lymph node metastases** Sens: 100% Spec: 68% PPV: 50% NPV: 100% Accu: 76%	**Primary tumour** Sens: 90% Spec: 26% PPV: 59% NPV: 69% Accu: 60% **Cervical lymph node metastases** Sens: 50% Spec: 88% PPV: 57% NPV: 85% Accu: 79%	NA
Hematologic Cancer								
Panebianco et al, 2019 [35]	Retrospective	62 patients (newly diagnosed HL)	FDG PET/CT	CeCT	Histology, consensus from a multidisciplinary team	NA	NA	PET/CT upstaged 9.7% (6/62) and downstaged 1.6% (1/62) of patients. Treatment strategy was modified in 8.1% (5/62)

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
								of patients.
Voltin et al, 2018 [36]	Retrospective	832 patients who underwent staging prior to treatment (newly diagnosed, biopsy-proven HL)	FDG PET or PET/CT or PET/MRI	Bone marrow biopsy	Bone marrow biopsy	**Bone marrow involvement** Sens: 95.0% Spec: 86.5% PPV: 14.7% NPV: 99.9%	NA	NA
Straus et al, 2018 [37]	Phase II trial (CALGB 50604)	149 patients who underwent interim response assessment after 2 cycles of ABVD (newly diagnosed, non-bulky stage I or II HL)	FDG PET/CT (interim PET-positive patients received 2 cycles of escalated BEACOPP and involved-field RT; interim PET-negative patients received 2 additional cycles of ABVD)	NA	Biopsy, follow-up	NA	NA	The 3-year PFS was significantly better for patients with a negative interim-PET than those with a positive interim-PET (91% vs. 66%; HR=3.84; 95% CI: 1.50 to 9.84; p=0.01).
Fuchs et al, 2019 [38]	Phase III RCT (HD16 trial)	1150 patients randomly assigned to either standard combined-modality treatment or PET-guided treatment that consisted of omitting IFRT for those patients with negative PET after 2 cycles of ABVD (newly	FDG PET/CT	NA	Clinical follow-up	NA	NA	For PET negative patients, the 5-year PFS was 93.4% for those who received combined-modality treatment and 86.1% for those who received ABVD alone (HR=1.78; 95%CI: 1.02 to 3.12; p=0.04, which included the predefined noninferiority margin of 3.01). The 5-year OS was 98.1% with combined-modality treatment and 98.4% with ABVD alone (HR=0.37; 95%CI: 0.10 to

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		diagnosed, early-stage, favourable HL)						1.37; p=0.12).
Kobe et al, 2018 [39]	Retrospective	722 patients who underwent interim response assessment after 2 cycles of escalated BEACOPP (newly diagnosed, advanced staged HL)	FDG PET/CT (interim PET-positive and PET-negative patients received 6 additional cycles of escalated BEACOPP)	NA	Clinical follow-up	NA	NA	There were no significant differences in 3-year PFS (92.0% vs. 92.2%, respectively; univariate HR=1.09; 95% CI: 0.61 to 1.95; p=0.8) and OS (98.0% vs. 97.6%, respectively; univariate HR=0.87; 95% CI: 0.33 to 2.31; p=0.8) between interim-PET positive patients (DS 3-4) and interim-PET negative patients (DS 1-2). However, the 3-year PFS (87.6% vs. 94.2%, respectively; univariate HR=2.27; 95% CI: 1.35 to 3.84; p=0.002) and OS (96.8% vs. 98.4%, respectively; univariate HR=2.60; 95% CI: 1.03 to 6.59; p=0.04) were significantly worst for patients with positive interim-PET (DS 4) than those with negative interim-PET (DS 1-3).
Bentur et al, 2019 [40]	Retrospective	78 elderly (age≥60) patients who underwent interim response assessment after 2-3 treatment cycles (newly diagnosed HL)	FDG PET/CT	NA	Clinical follow-up	**Predicting progression or death** PPV: 75% NPV: 76%	NA	The 5-year PFS (25% vs. 72%, respectively; p<0.0001; multivariate HR=8.5; 95% CI: 1.8 to 40.3; p=0.007) and OS (45% vs. 82%, respectively; p<0.0001; multivariate HR=6.9; 95% CI: 1.2 to 40.8; p=0.031) were significantly worst for patients with a positive interim-PET (DS 4-5) than those with a negative interim-PET (DS 1-3).

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Kitajima et al, 2019 [41]	Retrospective	80 patients who underwent interim response assessment after 2-4 cycles of R-CHOP or R-THP-COP and end of therapy assessment (newly diagnosed DLBCL)	FDG PET/CT	NA	Clinical follow-up	**Predicting relapse or progression** **Interim-PET** Sens: 33.3% Spec: 89.3% PPV: 57.1% NPV: 75.8% **End of therapy-PET** Sens: 25.0% Spec: 96.4% PPV: 75.0% NPV: 75.0%	NA	The 2-year PFS was significantly lower for patients with a positive interim-PET than those with a negative interim-PET (50.0% vs. 86.4%, p=0.0012). The 2-year PFS was also significantly lower for patients with a positive end of therapy-PET than those with a negative end of therapy-PET (25.0% vs. 84.7%, p<0.0001).
Nyilas et al, 2019 [42]	Retrospective	104 patients who underwent interim response assessment after 2-4 cycles of R-CHOP like regimen (newly diagnosed de novo DLBCL)	FDG PET/CT	International Prognostic Index	Clinical follow-up	**Prediction of OS** **Interim PET/CT** Sens: 52% Spec: 85% PPV: 48% NPV: 89% **End of treatment PET/CT** Sens: 53% Spec: 89% PPV: 50% NPV: 90% **Prediction of PFS** **Interim PET/CT** Sens: 32% Spec: 83% PPV: 48% NPV: 71% **End of treatment PET/CT** Sens: 47% Spec: 94% PPV: 78% NPV: 80%	NA	The 2-year PFS (67.4% vs. 79.9%, p=0.011) and OS (81.5% vs. 93.5%, p<0.001) were significantly inferior for patients with a positive interim-PET than those with a negative interim-PET.
Wang et al, 2019 [43]	Retrospective	101 patients who underwent pre-treatment staging (newly diagnosed extranodal natural killer/T-cell lymphoma)	FDG PET/CT	BMB	BMB	**Bone marrow infiltration** Sens: 100% Spec: 92.8% PPV: 36.4% NPV: 100% Accu: 93.1%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
Albano et al, 2019 [44]	Retrospective	229 patients who underwent staging (newly diagnosed, histologically proven mantel cell lymphoma)	FDG PET/CT	Bone marrow biopsy, gastrointestinal endoscopy	Clinical and imaging follow-up	**Bone marrow involvement** Sens: 27% Spec: 100% PPV: 100% NPV: 48% Accu: 57% -LR: 0.73 **Gastrointestinal tract involvement** Sens: 60% Spec: 99% PPV: 93% NPV: 90% Accu: 91% +LR: 54.21 -LR: 0.41	NA	NA
Ma et al, 2019 [45]	Retrospective	61 patients with suspicious enlarged superficial lymph nodes (lymphoma)	FDG PET/CT	CeCT, CeUS	Pathology	**Lymphomatous lymph nodes** Accu: 88.6% FN: 11.4%	**Lymphomatous lymph nodes** ***CeCT*** Accu: 80.7% FN: 19.3% ***CeUS*** Accu: 83.6% FN: 16.4%	NA
Metser, 2019 [46]	Prospective	850 patients who were considered for curative-intent first-line therapy (limited stage HL and aggressive NHL)	FDG PET/CT	CT	Follow-up	NA	NA	PET/CT helped upstage 17.6% (150/850) of patients and led to a change in planned therapy in 38.6% (224/580) of patients. Those with aggressive NHL treated with presumed limited stage at PET/CT had a significantly lower 1-year mortality compared with those treated with limited stage at CT (HR=0.51; 95% CI: 0.32 to 0.80; p=0.004).
Adams and Kwee, 2019 [47]	Meta-analysis	12 studies (1130 patients with lymphoma who initially achieved an	FDG PET or PET/CT	NA	Biopsy	**Post-treatment follow-up** **HL** Pooled FP: 35.2% **NHL**	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		end-of-treatment complete remission)				Pooled FP: 49.4%		
Melanoma								
Schaarschmidt et al, 2018 [48]	Retrospective	52 patients who underwent distant metastasis staging (malignant melanoma)	FDG PET/CT or PET/MRI	SPECT/CT guided SLNB	Histopathology	**Sentinel lymph node metastases** ***FDG PET/CT*** Sens: 17.7% Spec: 95.6% PPV: 50.0% NPV: 82.3% ***FDG PET/MRI*** Sens: 23.5% Spec: 96.9% PPV: 66.7% NPV: 82.3%	NA	NA
Dinnes et al, 2019 [49]	Meta-analysis	39 studies (5204 patients who underwent staging and restaging)	FDG PET/CT	US, CT/CeCT, MRI/CeMRI	Histology, clinical or imaging follow-up	**Nodal metastases before SLNB** Pooled Sens: 10.2% Pooled Spec: 96.5% **Any metastases** Pooled Sens: 92.6% Pooled Spec: 89.7%	**Nodal metastases before SLNB** ***US*** Pooled Sens: 35.4% Pooled Spec: 93.9%	NA
Groen et al, 2019 [50]	Retrospective	73 patients (stage III malignant cutaneous melanoma)	FDG PET/CT	Sentinel node procedure, lymph node dissection, lymph node biopsy	Histopathology	NA	NA	PET/CT upstaged 17.8% (13/73) of patients to stage IV who were additionally treated with immunotherapy.
Lee et al, 2019 [51]	Meta-analysis	11 studies (1347 patients treated for malignant melanoma)	FDG PET or PET/CT	NA	Histopathology, clinical follow-up	**Recurrence** Pooled Sens: 94% Pooled Spec: 91% Pooled +LR: 10.4 Pooled –LR: 0.06 Pooled DOR: 162 AUC: 0.96	NA	NA
Lewin et al, 2018 [52]	Retrospective	170 patients who underwent postoperative surveillance (stage 3 melanoma)	FDG PET/CT	Brain MRI	Histology, clinical or imaging follow-up	**Recurrence** Sens: 70% Spec: 87% PPV: 80% NPV: 80%	NA	NA
Neuro-Oncology								
Suh et al, 2018 [53]	Meta-analysis	20 studies (728 patients with brain metastasis	FDG PET or PET/CT	MRI	Histopathology or clinicoradiolog	**Differentiating tumour recurrence from radiation**	**Differentiating tumour recurrence from radiation**	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		after stereotactic radiosurgery)			y	**necrosis** Pooled Sens: 83% Pooled Spec: 88%	**necrosis** Pooled Sens: 84% Pooled Spec: 88% AUC: 0.92	
Non-FDG Tracers ^{11}C/^{18}F-Choline								
Signore et al, 2019 [54]	Meta-analysis	9 studies (283 patients with hepatocellular carcinoma)	^{11}C/^{18}F-Choline PET or PET/CT	CT, MRI	Histology, non-invasive criteria, multidisciplinary workflow, follow-up	**Malignant lesions (patient-based)** Pooled DR: 83% **(lesion-based)** Pooled DR: 79%	NA	NA
Kim et al, 2019 [55]	Meta-analysis	7 studies (627 patients with newly diagnosed prostate cancer)	^{18}F-FCH PET/CT	NA	Not specified	**Preoperative lymph node staging** Pooled Sens: 57% Pooled Spec: 94% Pooled +LR: 10.2 Pooled –LR: 0.46 Pooled DOR: 22 AUC: 0.90	NA	NA
^{68}Ga-DOTA-(TATE, NOC, TOC)								
Han et al, 2019 [56]	Meta-analysis	9 studies (215 patients with pheochromocytoma and paraganglioma)	^{68}Ga-DOTA-TATE/NOC/TOC PET or PET/CT	123/131I-MIBG scintigraphy	Histopathology, clinical or imaging follow-up	**Malignant lesions (lesion-based)** Pooled DR: 93%*	**Malignant lesions (lesion-based)** Pooled DR: 38%*	NA
Tierney et al, 2019 [57]	Retrospective	50 patients (histologically proven or suspected NETs)	^{68}Ga-DOTA-TATE PET/CT	CT, MRI	Pathology, chart review comparison	NA	NA	^{68}Ga-DOTA-TATE PET/CT changed management in 66% (33/50) of patients (24—intermodality changes, 9—intramodality changes).
Amyloid								
de Wilde et al, 2018 [58]	Prospective	507 patients who underwent routine diagnostic dementia workup (unselected memory clinic cohort)	^{18}F-florbetaben PET	Medical and informant-based history, neurological examinations, neuropsychological testing, basic laboratory testing, MRI	Consensus at weekly multidisciplinary meetings	NA	NA	Amyloid PET changed the suspected etiological diagnosis for 24.7% (125/507) of patients. Subsequently, management was changed in 24.3% (123/507) of patients.
Fantoni et al, 2018 [59]	Systematic review	12 studies (1142 patients with cognitive complaints)	^{18}F-florbetaben PET, ^{18}F-flutemeta	Clinical history, neuropsychological tests, CT, MRI, FDG PET,	Clinical diagnostic criteria	NA	NA	Amyloid PET contributed to diagnostic revision in 31.3% (357/1142) of patients. Overall

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
			mol PET, ^{18}F-florbetapir PET, ^{11}C-PiB PET, ^{18}F-NAV4694 PET	cerebrospinal fluid				management change occurred in 72.2% (534/740) of patients.
Shea et al, 2018 [60]	Meta-analysis	13 studies (1489 patients with cognitive impairment attending memory clinics)	^{18}F-florbetaben PET, ^{18}F-flutemetamol PET, ^{18}F-florbetapir PET, ^{11}C-PiB PET, ^{18}F-NAV4694 PET	NA	Follow-up	NA	NA	Amyloid PET led to a change in diagnosis in 35.2% (524/1489) of patients and a change in management in 59.6% (364/611) of patients.
^{68}Ga-PSMA								
Lengana et al, 2018 [61]	Prospective	113 patients (biopsy-proven prostate cancer)	^{68}Ga-PSMA-11 PET/CT	99mTc-MDP bone scintigraphy	Histology, clinical follow-up	**Bone metastases** Sens: 96.2%* Spec: 100% PPV: 100% NPV: 98.9% Accu: 99.1%*	**Bone metastases** Sens: 73.1%* Spec: 87.4% PPV: 63.3% NPV: 91.6% Accu: 84.1%*	^{68}Ga-PSMA-11 PET/CT detected soft tissue metastases in 12.4% (14/113) of patients who had negative bone scans.
Kumar et al, 2019 [62]	Prospective	15 patients with lower urinary tract symptoms and serum PSA between 4 and 20 ng/ml (prostate cancer)	^{68}Ga-PSMA-11 PET/CT	Serum PSA, mpMRI	Biopsy	**Diagnosis** Sens: 88.8% Spec: 66.6% PPV: 80.0% NPV: 80.0% Accu: 80.0%	**Diagnosis** ***Serum PSA*** Sens: 33.3% Spec: 100% PPV: 50.0% NPV: 100% Accu: 60.0% ***mpMRI*** Sens: 62.5% Spec: 71.4% PPV: 62.5% NPV: 71.4% Accu: 66.6%	NA
Calais et al, 2019 [63]	Retrospective	73 patients who underwent initial staging before intended radical prostatectomy	^{68}Ga-PSMA-11 PET/CT	CT	Consensus clinical target volumes	NA	NA	^{68}Ga-PSMA-11 PET/CT had a potential major impact on definitive radiotherapy planning in 16.4% (12/73) of patients whose radiotherapy fields

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		with pelvic lymph node dissection (intermediate- or high-risk prostate cancer)						covered the prostate, seminal vesicles, and pelvic lymph nodes.
Onal et al, 2019 [64]	Retrospective	185 patients to be treated with definitive intensity-modulated radiotherapy (intermediate- or high-risk prostate cancer)	^{68}Ga-PSMA PET/CT	CT, bone scintigraphy	Histopathology, consensus from an interdisciplinary team	NA	NA	^{68}Ga-PSMA PET/CT changed the staging of 27.6% (51/185) of patients (20—downstaging, 31—upstaging). Radiotherapy planning changed in 13.0% (24/185) of patients (20—change in radiotherapy field, 4—radiotherapy aborted).
Kuten et al, 2019 [65]	Retrospective	52 patients who underwent treatment response assessment (metastatic prostate cancer)	^{68}Ga-PSMA-11 PET/CT	Serum PSA level	Clinical follow-up	NA	NA	^{68}Ga-PSMA-11 PET/CT guided further therapeutic management in 73.3% (22/30) of patients.
^{18}F-NaF								
Sheikhbahaei et al, 2019 [66]	Meta-analysis	14 studies (574 patients with prior clinical, laboratory or imaging suspicion of bone metastases)	^{18}F-NaF PET/CT	99mTc-bone scintigraphy, 99mTc-SPECT, DWI-MRI	Histopathology, clinical or imaging follow-up	**Bone metastases (patient-based)** Pooled Sens: 98% Pooled Spec: 90% Pooled +LR: 6.64 Pooled –LR: 0.07 Pooled DOR: 123.2 AUC: 0.97 Q index: 0.92 **(lesion-based)** Pooled Sens: 97% Pooled Spec: 84% Pooled +LR: 7.35 Pooled –LR: 0.05 Pooled DOR: 206.78 AUC: 0.97 Q index: 0.93	**Bone metastases (patient-based)** ***99mTc-bone scintigraphy*** Pooled Sens: 83% Pooled Spec: 62% Pooled DOR: 13.7 AUC: 0.84 ***99mTc-SPECT*** Pooled Sens: 87% Pooled Spec: 75% Pooled DOR: 17.7 AUC: 0.90 ***DWI-MRI*** Pooled Sens: 83% Pooled Spec: 90% Pooled DOR: 32.4 AUC: 0.95 **(lesion-based)** ***99mTc-bone scintigraphy***	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
							Pooled Sens: 51% Pooled Spec: 81% Pooled DOR: 4.3 AUC: 0.77 ***99mTc-SPECT*** Pooled Sens: 69% Pooled Spec: 81% Pooled DOR: 8.63 AUC: 0.80	
^{18}F-FACBC								
Laudicella et al, 2019 [67]	Meta-analysis	15 studies (1226 patients with prostate cancer)	^{18}F-FACBC PET/CT	NA	Pathology, other imaging confirmations	**Primary and recurrent disease (patient-based)** Pooled Sens: 86.3% Pooled Spec: 75.9% Pooled +LR: 4.56 Pooled –LR: 0.34 Pooled DOR: 16.45 **(region-based)** Prostatic bed Pooled Sens: 90.4% Pooled Spec: 45.1% Pooled +LR: 1.60 Pooled –LR: 0.22 Pooled DOR: 8.03 **Extra-prostatic regions** Pooled Sens: 76.5% Pooled Spec: 88.9% Pooled +LR: 6.02 Pooled –LR: 0.25 Pooled DOR: 24.82	NA	NA
Suzuki et al, 2019 [68]	Prospective Phase II	28 patients who were scheduled for regional lymph node dissection (prostate cancer)	^{18}F-FACBC PET/CT	CeCT	Histopathology	**Regional lymph node metastases (patient-based)** Sens: 66.7% Spec: 86.4% PPV: 57.1% NPV: 90.5% Accu: 82.1% **(node-based)** Sens: 57.1% Spec: 84.8% PPV: 44.4% NPV: 90.3% Accu: 80.0%	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
^{18}F-FDOPA								
Xiao et al, 2019 [69]	Meta-analysis	19 studies (589 patients with glioma)	^{18}F-FDOPA PET or PET/CT	NA	Histopathology, clinical and imaging follow-up	**Diagnosis** Pooled Sens: 90% Pooled Spec: 75% Pooled +LR: 2.84 Pooled –LR: 0.15 Pooled DOR: 24.05 AUC: 0.85 **Grading** Pooled Sens: 88% Pooled Spec: 73% Pooled +LR: 2.90 Pooled –LR: 0.16 Pooled DOR: 25.87 AUC: 0.89	NA	NA
Pediatric Cancer								
Cistaro et al, 2019 [70]	Retrospective	224 patients who underwent initial staging (newly diagnosed HL)	FDG PET/CT	BMB	Clinical and imaging follow-up	**Bone marrow involvement** Sens: 96% Spec: 97% PPV: 80.6% NPV: 99.5%	**Bone marrow involvement** Sens: 38% Spec: 100% PPV: 100% NPV: 92.5%	NA
Sarcoidosis								
Milojevic et al, 2019 [71]	Prospective	38 patients (head and neck sarcoidosis)	FDG PET/CT	Medical examination, laboratory analyses, CT, MRI, pulmonary spirometry, heart US, ECG	Histopathology	NA	NA	PET/CT changed the therapy of 26.3% (10/38) of patients (8—received higher corticosteroid doses, 2—received methotrexate along with pronisone).
Sarcoma								
Liu et al, 2019 [72]	Meta-analysis	26 studies (798 patients with osteosarcoma)	FDG PET or PET/CT	NA	Histopathology, follow-up	**Primary lesion** Pooled Sens: 100% **Recurrence** Pooled Sens: 91% Pooled Spec: 93% Pooled +LR: 7.36 Pooled –LR: 0.14 Pooled DOR: 63.98 AUC: 0.95 Q index: 0.88 **Lung metastases** Pooled Sens: 81% Pooled Spec: 94% Pooled +LR: 8.13 Pooled –LR: 0.26	NA	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						Pooled DOR: 48.85 AUC: 0.93 Q index: 0.86 **Bone metastases** Pooled Sens: 93% Pooled Spec: 97% Pooled +LR: 9.81 Pooled –LR: 0.08 Pooled DOR: 174.19 AUC: 0.98 Q index: 0.94 **Distant metastases** Pooled Sens: 90% Pooled Spec: 96% Pooled +LR: 13.81 Pooled –LR: 0.13 Pooled DOR: 125.67 AUC: 0.96 Q index: 0.91		
Jo et al, 2019 [73]	Meta-analysis	13 studies (602 patients with chondrosarcoma)	FDG PET or PET/CT	Tc-99m MDP, Thallium-201 scintigraphy, Tc99m-DMSA	Histopathology, clinical and imaging follow-u	**Diagnosis** Pooled Sens: 75% Pooled Spec: 90% Pooled DOR: 62.04	**Diagnosis** ***Tc-99m MDP*** Pooled Sens: 95% Pooled Spec: 4% Pooled DOR: 1.13 ***Thallium-201 scintigraphy*** Pooled Sens: 31% Pooled Spec: 91% Pooled DOR: 4.94 ***Tc99m-DMSA*** Pooled Sens: 100% Pooled Spec: 47% Pooled DOR: 23.92	NA
Albano et al, 2019 [74]	Retrospective	41 patients who underwent post therapy surveillance; 73 PET/CT scans (asymptomatic or suspected recurrence of uterine sarcoma)	FDG PET/CT	US, MRI, CeCT/CT	Histopathology, clinical and imaging follow-up	**Recurrence (study-based)** Sens: 88% Spec: 98% PPV: 97% NPV: 91% Accu: 93%	NA	PET/CT influenced the management in 19.5% (8/41) of patients (6—avoided unnecessary treatment, 2—initiated chemotherapy).
Thoracic Cancer								
Dyas et al, 2018 [75]	Retrospective	1444 patients (NSCLC)	FDG PET or PET/CT	Chest CT	Pathology, biopsy	**Stage I** Sens: 77% Spec: 70%	**Stage I** Sens: 76% Spec: 79%	NA

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
						PPV: 73% NPV: 74% Accu: 74% **Stage II** Sens: 43% Spec: 88% PPV: 39% NPV: 89% Accu: 80% **Stage III** Sens: 46% Spec: 93% PPV: 67% NPV: 84% Accu: 81% **Stage IV** Sens: 61% Spec: 94% PPV: 44% NPV: 97% Accu: 91%	PPV: 77% NPV: 78% Accu: 77% **Stage II** Sens: 48% Spec: 89% PPV: 43% NPV: 91% Accu: 83% **Stage III** Sens: 58% Spec: 88% PPV: 60% NPV: 87% Accu: 80% **Stage IV** Sens: 82% Spec: 96% PPV: 75% NPV: 97% Accu: 94%	
Gambazzi et al, 2019 [76]	RCT	96 patients who had completed a curative-intent treatment and underwent post-treatment surveillance (NSCLC)	FDG PET/CT (n=50)	CeCT (n=46)	Histopathology, additional investigations	**Recurrence** Sens: 88% Spec: 62% PPV: 56%	**Recurrence** Sens: 93% Spec: 72% PPV: 64%	NA
Basso Dias et al, 2019 [77]	Meta-analysis	6 studies (651 patients; 728 indeterminate pulmonary lesions)	FDG PET/CT	DWI-MRI	Histopathology, imaging follow-up	**Differentiating between malignant and benign lesions (lesion-based)** Pooled Sens: 78%* Pooled Spec: 81% Pooled PPV: 79% Pooled NPV: 77% Pooled +LR: 4.1 Pooled –LR: 0.28 Pooled DOR: 15* AUC: 0.86*	**Differentiating between malignant and benign lesions (lesion-based)** Pooled Sens: 83%* Pooled Spec: 91% Pooled PPV: 89% Pooled NPV: 83% Pooled +LR: 9.1 Pooled –LR: 0.18 Pooled DOR: 50* AUC: 0.93*	NA
Kitajima et al, 2019 [78]	Retrospective	50 patients who underwent post-surgery surveillance (malignant	FDG PET/CT	CeCT	Histology, cytology, clinical and imaging follow-up	**Tumour recurrence** Sens: 90.0%* Spec: 80.0% PPV: 94.7% NPV: 66.7%	**Tumour recurrence** Sens: 75.0* Spec: 90.0% PPV: 96.8% NPV: 47.4%	PET/CT impacted the management of 28.0% (14/50) of patients (8—initiated chemotherapy, 3—initiated radiotherapy,

Citation	Study Type	Population	PET Type	Conventional Intervention	Reference Standard	Diagnostic Performance (PET)	Diagnostic Performance (Conventional Intervention)	Change in Patient Management
		pleural mesothelioma)				Accu: 88.0% AUC: 0.915* **Thoracic recurrence** Sens: 91.4% Spec: 86.7% PPV: 94.1% NPV: 81.3% Accu: 90.0%* AUC: 0.946* **Lymph node involvement** Sens: 80.0% Spec: 100% PPV: 100% NPV: 88.2% Accu: 92.0%* AUC: 0.953 **Distant metastasis** Sens: 91.3% Spec: 85.2% PPV: 84.0% NPV: 92.0% Accu: 88.0% AUC: 0.957*	Accu: 78.0% AUC: 0.805* **Thoracic recurrence** Sens: 82.9% Spec: 60.0% PPV: 82.9% NPV: 60.0% Accu: 76.0%* AUC: 0.837* **Lymph node involvement** Sens: 55.0% Spec: 96.7% PPV: 91.7% NPV: 76.3% Accu: 80.0%* AUC: 0.889 **Distant metastasis** Sens: 73.9% Spec: 81.5% PPV: 77.3% NPV: 78.6% Accu: 78.0% AUC: 0.852*	2—underwent resection, 1—new treatment modality).

*p<0.05

‡Significant difference with PET/MRI (p<0.05)

µLymph nodes from upper diaphragm, brain, or multiple recurrences

Abbreviations: ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine combination therapy; Accu, accuracy; AUC, area under the curve; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BMP, basic metabolic panel; CA-125, cancer antigen 125; ^{11}C-Choline, carbon-11-choline contrast; ^{11}C-PiB, Carbon-11-labelled Pittsburgh compound B; CeCT, contrast-enhanced computed tomography; CeUS, contrast-enhanced ultrasound; CI, confidence interval; CT, computerized tomography; CT w CI, computerized tomography with contrast imaging; DLBCL, diffuse large B-cell lymphoma; DMFS, distant metastasis-free survival; DOR, duration of response; DS, Deauville score; DWI-MRI, diffusion-weighted magnetic resonance imaging; ECG, electrocardiogram; EEG, electroencephalogram; EUS, Endoscopic ultrasound; ^{18}F-Choline, fluoromethylcholine; ^{18}F-FCH, ^{18}F-fluorocholine; ^{18}F-NaF, fluorine 18–sodium fluoride; FDG, fluorodeoxyglucose; F-FACBC, anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid; F-FDOPA, 6-(18)F-fluoro-l-dopa; FNA, fine needle aspiration; FP, 5-fluorouracil plus cisplatin; ^{68}Ga-DOTA-NOC, Gallium-68-1,4,7,10-tetraazacyclododecane-1,4,7,10-tet-raacetic acid-1-Nal3-octreotide; ^{68}Ga-DOTA-TATE, Gallium-68-dodecanetetraacetic acid-Tyr3-octreotate; ^{68}Ga-DOTA-TOC, Gallium-68-edotretide; ^{68}Ga-PSMA-11, Gallium-68-labelled prostate-specific membrane antigen 11; HL, Hodgkin lymphoma; HR, hazard ratio; IMZ-SPECT, 123I-iomazenil single-photon emission computerized tomography; +LR, positive likelihood ratio; -LR, negative likelihood ratio; MDCT, multidetector computed tomography; 123I-MIBG, I-Metaiodobenzylguanidine labelled with Iodine-123; 131I-MIBG, I-Metaiodobenzylguanidine labelled with Iodine-131; mpMRI, multi-parametric magnetic resonance imaging; MRI, magnetic resonance imaging; 99mTc-MDP, technetium 99m-methyl diphosphonate; 99mTc-SPECT, technetium 99m-single photon emission computed tomography; NA, not applicable; NETs, neuroendocrine tumours; NHL, non-Hodgkin lymphoma; NPV, negative predictive value; NSCLC, non-small-cell lung carcinoma; OS, overall survival; PET, positron emission tomography; PFS, progression free survival; PPV, positive predictive value; PSA, prostate specific antigen; R-CHOP, monoclonal antibody rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone combination therapy; RCT, randomized controlled trial; RR, relative risk; RT, radiation therapy; R-THP-COP, monoclonal antibody rituximab, pirarubicin, cyclophosphamide, vincristine, and prednisolone combination therapy; Sens, sensitivity; SLNB, sentinel lymph node biopsy; Spec, specificity; SPECT, single-photon emission computerized tomography; SULpeak, peak standardized uptake values corrected for lean body mass; Tc-99m-DMSA, technetium 99m-2,3 dimercaptosuccinic acid); Tg, thyroglobulin; US, ultrasound; VEEG, video electroencephalograph; vs, versus; WBS, whole-body scan; WOC, without contrast